rejected under 35 U.S.C. §102(a) as unpatentable over A-Mohammadi et al. (1998) *Gene Therapy* 5:76-84 ("Mohammadi"); (5) claims 1, 12-14 and 24-27 were rejected under 35 U.S.C. §102(b) as unpatentable over Hofmann et al. (1996) *Proc. Natl. Acad. Sci.* 93:5185-5190 ("Hofmann"); (6) claims 1-4, 7, 8, 11-17, 20-23 and 25-27 were rejected under U.S.C. §102(b) as unpatentable over Lai et al. (1995) *DNA and Cell Biol.* 14:643-651 ("Lai"); and (7) claims 1, 5, 7, 8 and 12 were rejected under 35 U.S.C. §102(b) as unpatentable over Laube et al. (1994) *Human Gene Therapy* 5:853-862 ("Laube"). These rejections are traversed for reasons discussed below.

Overview of the Amendments:

Applicant, by way of this amendment, has amended claims 1 and 7 to recite the invention with greater particularity. More specifically, claim 1 has been amended to recite methods for obtaining expression of an antigen of interest, and to expressly state that the antigen coding sequence is expressed in the host cells. Support for this claim amendment can be found throughout the specification and claims as originally filed.

Claim 7 has been amended to recite methods for obtaining an antigen of interest, wherein the antigen is a full length protein. Support for this amendment can be found throughout the specification and claims as originally filed and particularly at page 12, lines 20-25 of the detailed description.

Finally, claim 25 has been recited to recite a nucleic acid construct containing a minimal promoter according to the present invention operably linked to a coding sequence for an antigen of interest. Support for this amendment can be found throughout the specification and claims as originally filed.

Accordingly, applicant submits that no new matter has been added by way of the above-described claim amendments and the entry thereof is respectfully requested.

Election of Claims:

The Office has required election of one of the following groups of claims:

Group I: Claims 1-8, 11-17 and 20-27, drawn to methods for obtaining expression of an antigen of viral, bacterial, parasite or fungal pathogen, coated particles comprising a nucleic acid construct with a minimal promoter sequence operably linked to a coding sequence for said antigens, a particle accelerating device for delivering particles coated with or comprising said constructs, and an isolated minimal promoter sequence and a nucleic acid construct containing the same, classified in class 514, subclass 44;

Group II: Claims 1-7, 9, 11-16, 18 and 20-27, drawn to methods for obtaining expression of a tumor specific antigen or an antigen associated with an autoimmune disease, coated particles comprising a nucleic acid construct with a minimal promoter sequence operably linked to a coding sequence for said antigens, a particle accelerating device for delivering particles coated with or comprising said constructs, and an isolated minimal promoter sequence and a nucleic acid construct containing the same, classified in class 514, subclass 44; and

Group III: Claims 1-7, 10-16 and 19-27, drawn to methods for obtaining expression of an antigen comprising a B-cell epitope or a T-cell epitope, coated particles comprising a nucleic acid construct with a minimal promoter sequence operably linked to a coding sequence for said antigens, a particle accelerating device for delivering particles coated with or comprising said constructs, and an isolated minimal promoter sequence and a nucleic acid construct containing the same, classified in class 514, subclass 44.

Applicant hereby confirms the election to prosecute the claims of Group I, claims 1-8, 11-17 and 20-27, with limited traverse. Applicant expressly reserves his right under 35 USC §121 to file a divisional application directed to the nonelected subject matter during the pendency of this application.

Applicant traverses the requirement for restriction on the following ground. The Office has described the inventions of Groups I-III as drawn to, *inter alia*, "a particle accelerating device for delivering the same coated particles" (see Office Action pages 2 and 3). This is only partially correct, as applicant's recited invention covers particle accelerating devices for delivering both coated particles (see page 20, lines 11-23 of the specification) as well as particulate nucleic acid compositions (see page 20, line 24 through page 21, line 4 of the specification). This distinction has been addressed in applicant's above-recited definitions of the groups, and election of Group I is made on the basis that both types of particle delivery techniques are included. Should the Office desire to create a new group drawn to this second type of particle delivery, applicant hereby requests that a new restriction requirement be made in a new non-final Office Action.

The Rejections under 35 U.S.C. §112, first paragraph:

Claims 1-5, 7, 8 and 11-14 were rejected under 35 U.S.C. §112, first paragraph, as nonenabled. In particular, the Office acknowledges that applicant's specification "is enabling for an *in vitro* method of obtaining expression in mammalian cells of a polypeptide [that] is an antigen of a viral, bacterial, parasite or fungal pathogen and *in vivo* or autologous *ex vivo* methods of obtaining expression of the same antigen in non-human cells," but objects that this enabling disclosure "does not reasonably provide enablement for any and all *in vivo* or *ex vivo* methods of expressing any and all polypeptides of interest in any and all mammalian cells for the purposes of genetic therapy and nucleic acid immunization."

The Office also acknowledges that applicant has described the construction of Hepatitis B surface antigen expression cassettes driven by the minimal promoter systems of the present invention and that these were administered to mice and shown

to have significant efficacy as evidenced by enhanced antibody titer when compared against full-length promoter systems. Office Action at page 5. However, the Office objects that this evidence "cannot be extrapolated" for all claimed method for gene therapy and nucleic acid immunization purposes. A number of specific grounds are then expressed over pages 6-10, relating either to gene therapy or nucleic acid immunization. Applicant respectfully traverses the rejection for the following reasons.

Initially, applicant notes that the Office has defined the elected invention as being drawn to methods for obtaining expression of antigens from viral, bacterial, parasite or fungal pathogens (see page 2 of the Office Action for the definition of the Group I claims), i.e., methods for nucleic acid immunization. However, in the arguments in support of the instant rejection, the Office spends the bulk of its time discussing gene therapy, wherein applicant's invention is clearly treated as including delivery of much more than nucleic acid immunization.

Applicant submits that there is a clear distinction between gene therapy and nucleic acid immunization. Gene therapy seeks to correct a genetic deficiency in a host genome using by inserting a functioning gene that expresses a necessary or desired gene product that is otherwise defective or missing from the subject being treated. Stable integration, the ability to achieve sustained expression, and the identity of the target cells themselves are thus all issues with respect to gene therapy. By contrast, nucleic acid immunization merely seeks to provide, for a short time, expression of an antigen sequence that is associated with a pathogen, wehrein expression can be in any cell type e.g., skin, muscle, etc. This sort of antigen expression within host cells resembles natural infection with the pathogen, and brings about an immune response against the pathogen. Since the antigen sequence is from a pathogen, one does not want to have stable integration and sustained expression of the antigen sequence. Accordingly, perceptions regarding the shortcomings of gene therapy are not appropriately applied against nucleic acid immunization techniques.

Applicant respectfully requests that the Office examine the elected claims in accordance with it's definition of those claims as helpfully set forth by the

restriction requirement. More particularly, applicant requests that the Office confine its grounds of rejection to those issues that relate to nucleic acid immunization and not gene therapy. In order to help facilitate this focus, applicant has amended claim 1 to better match the Office's definition of the Group I invention.

Turning now to the Office's specific objections, on page 6, the first full paragraph, the Office has objected that human gene therapy is "an immature science with limited understanding of gene regulation and disease models for preclinical studies," and that the field is limited by "lack of long term and stable gene expression and most importantly efficient gene delivery to target tissues." Applicant submits that this objection is specific to gene therapy and does not properly apply to the elected claims.

In the paragraph bridging pages 6 and 7, the Office objects that insufficient guidance and examples are provided by applicant's specification to overcome these "hurdles in gene therapy." Applicant submits that this objection is also specific to gene therapy and does not properly apply to the elected claims.

In the paragraph bridging pages 7 and 8, the Office objects that "vector targeting *in vivo* to desired cells continues to be unpredictable and inefficient." This objection is supported by reference to the Verma article (Verma et al. (1997) *Nature* 389:239-242) which relates to gene therapy. Applicant submits that this objection is specific to gene therapy and does not properly apply to the elected claims.

In the paragraph bridging pages 8 and 9, the Office objects that "the specification fails to provide direction and examples showing that immune-mediated rejection of genetically modified allogeneic and xenogeneic cells can be suppressed or eliminated in order to obtain therapeutic effects." This objection is supported by reference to the Gerson article (Gerson (1999) *Nature Medicine* 5:262-264) which relates to use of stem cells for human gene therapy. Applicant submits that this objection is specific to gene therapy and does not properly apply to the elected claims.

In the paragraph bridging pages 9 and 10, the Office objects that "the state of the art [with respect to nucleic acid immunization] is new and unpredictable at the effective filing date of the present invention." To support this objection, the Office

references a 1997 article to Chattergoon et al. (1997) *FASEB* 11:753-763, particularly the passage stating "there is little evidence that the immune response induced by these vaccines will be *completely protective* against any human pathogen," Chattergoon at page 762 (emphasis added). The Office goes on to assert " it is impossible to predict whether an untested antigen of an infectious pathogen will elicit a *protective immune response*" (emphasis added), and "one skilled in the art would have recognized that results observed in animal [models] are not predictive of outcome or efficacy in applications in other species of animal or in humans." To support this last assertion, the Office references McCluskie et al. (1999) *Molecular Medicine* 5:287-300, particularly the passage "it is probably safe to say that any vaccine that works in a human will work in a mouse, but not necessarily *vice versa*." For these reasons, the Office concludes that applicant's specification is not sufficiently enabling, and that it would entail undue experimentation to carry out applicant's recited methods. Applicant respectfully traverses.

The Office has raised two issues: (1) the first relating to it's perception that it is unpredictable whether or not a nucleic acid vaccine will produce a *completely protective* immune response; and (2) the second relating to it's perception that mouse models are not art recognized as being predictive of vaccine potential in humans. Applicant submits that both of these issues are improperly raised against the recited invention.

With regard to the Office's first issue, applicant respectfully submits that the Office seems to have equated applicants' recited "obtain expression of an antigen of interest" with a "bring about a *completely protective* immune response." This reading of the claims is simply not supported by any fair reading of applicant's specification and claims. To summarize, the Office has acknowledged that applicant has indeed enabled methods for obtaining expression of an antigen of interest using numerous different minimal promoter systems, and further that these compositions were able to bring about a significant and enhanced immune response when administered to mice. See pages 4 and 5 of the Office Action. In sum, applicant has adequately enabled his recited methods throughout their scope. However, the level of

enablement that the Office seems to be seeking would be: exactly how one must use applicant's methods to absolutely and completely protect against infection. Applicant is unaware of any statutory or other legal basis for this requirement. In fact, applicant submits that his only obligation under Section 112 is merely to provide a specification that enables one skilled in the art to make and use the invention as claimed. Applicant submits that he has met this burden, and that this basis for rejection is thus improper.

With respect to the Office's second issue, applicant respectfully submits that the Office seems to imply that those skilled in the art do not consider mouse models to appropriate systems for assessing vaccine compositions. This position flies in the face of over 30 years of immunological and vaccine research which has been and continues to be carried out in mouse animal model systems. If the Office is correct, this would mean that an awful lot of time, money has been wasted over the last thirty years. Applicant submits that the Office is more likely implying that mouse model systems are not 100% predictive of the ability of a candidate composition to provide *complete protective immunity* in other animals, but, as noted above, this is not what is required by the claims. Once again, claim 1 recites a method for obtaining expression of an antigen of interest, not a method for providing absolute protective immunity.

The Office has acknowledged that applicant has shown markedly superior results with several of his recited minimal promoter systems in an art-recognized animal model system. In this regard, it is useful to note that reference cited by the examiner to question the appropriateness of the mouse model system (McCluskie) reports mouse studies to assess a nucleic acid vaccine composition. For this reason, this second basis for the instant rejection is deemed improper.

Once again, applicant draws the Office's attention to the language of the claims, where methods for obtaining expression of an antigen sequence are recited. Applicant has not recited a method for absolutely preventing all infection and disease here. If one of skill in the art wishes to carry out this method, all that is needed is for the encoded antigen to be expressed. In looking through the Office's grounds for this

rejection, it is again submitted that the Office is applying an extra-statutory standard for enablement against this claim.

With regard to the Offices objection that undue experimentation is required, applicant notes that the mere fact that some experimentation may be required to practice the invention throughout its entire scope does not necessarily make it "undue," particularly when the level of skill in the art is typically high, and such experimentation is routinely carried out. It is well settled that satisfaction of the enablement requirement of Section 112 is not precluded by the necessity for some experimentation such as routine screening. The prohibition is against "undue" experimentation, not merely "experimentation." *In re Angstadt*, 190 USPQ 214 (CCPA 1976). The prohibition certainly does not require applicant to ensure that "protective immunity is always achieved with the claimed invention without undue experimentation." If the Office intends to maintain this standard or review, applicants request that the Office provide a citation to support this requirement.

That applicant has indeed taught how to practice his recited methods is manifest in the actual working models provided in the instant specification. Various genetic constructs have been delivered into host cells *in vivo*, properly expressed, and appropriate immune responses have been detected in the animal subjects. See, e.g., applicant's working examples.

Accordingly, to properly assess enablement of claims 1-5, 7-8 and 11-14, the Office needs to balance the detailed disclosure provided by applicant's specification (which disclosure has already been acknowledged by the Office), the presence of actual working examples (carried out in art-recognized animal models) in that specification, and the very high level of skill in the art of molecular biology and immunology, against the Office's perceived notion of any necessity for experimentation. *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). In this regard, applicant respectfully submits that the Office has failed to provide sufficient evidence of unpredictability relevant to the claims properly under examination (and merely requiring expression of the antigen of interest). The Office has also failed to establish that a proper consideration of the other Wands factors would support its theory of

nonenablement. In fact, applicant submits that a proper balance of these factors comes out clearly in the favor of enablement.

For all of the foregoing reasons, then, applicant submits that the rejection of claims 1-5, 7-8 and 11-14 under 35 U.S.C. §112, first paragraph, is improper. Reconsideration and withdrawal is thus respectfully requested.

Claim 6 stands rejected under 35 U.S.C. §112, first paragraph, as nonenabled. The Office asserts that the claim, being "drawn to a method of obtaining expression in mammalian cells ... wherein the subject is human" is nonenabled for the reasons cited in the preceding section (the rejection of claims 1-5, 7-8 and 11-14 under 35 U.S.C. §112, first paragraph). Applicant traverses the instant rejection for the same reasons present above. Reconsideration and withdrawal of the rejection of claim 6 under 35 U.S.C. §112, first paragraph, is thus respectfully requested.

The Rejections under 35 U.S.C. §112, second paragraph:

Claims 1-8, 11-17 and 20-27 were rejected under 35 U.S.C. §112, second paragraph, as indefinite. Initially, the Office has objected that claim 1 (and those claims dependent thereon) is incomplete for omitting an essential element. In particular, the Office has objected that the claim has a gap between transfer of the nucleic acid sequence into the host cell and expression of the coding sequence. Clarification was requested.

In response, applicant draws the Office's attention to the amendment to claim 1 wherein the express step of expressing the antigen sequence after transferring the nucleic acid sequence into the cell is now added. Reconsideration and withdrawal of the rejection of claims 1-8, 11-17 and 20-27 under 35 U.S.C. §112, second paragraph, is thus respectfully requested.

The Office has also objected to the use of the term "minimal promoter" as used in claims 1, 15, 24 and 25 on the basis that it is "unclear" and "appears to read on any promoter." Clarification has been requested. Applicant respectfully traverses the rejection for the following reasons.

Applicant submits that the term "minimal promoter" is indeed clear definite. Initially, applicant draws the Office's attention to page 10, lines 7-26, wherein the term has been clearly defined. As can be seen the term does not "read on any promoter," rather the term intends only those promoter sequences that have been stripped and separated from their native enhancer sequences. Applicant notes that the primary purpose of Section 112's requirement for clarity and precision is to ensure that the public is informed of the metes and bounds of the claimed invention. Applicant also notes that definiteness of claim language must be analyzed, not in a vacuum, but in light of: (1) the content of the disclosure provided by the specification; (2) the teachings of the prior art; and (3) the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made. Applicant submits that he his specification provides "broad disclosure" regarding the nature and identity of the "minimal promoters" used in the invention, as well as the sorts of antigen sequences that can be combined with these minimal promoters. The definiteness of applicant's claims must be assessed in light of this broad disclosure, the teachings of the prior art, and the sort of interpretation that one of ordinary skill in the art would give. Applicant submits that when the term "minimal promoter" is assessed in light of these factors, it is clear that the claims meet the requirements of Section 112, second paragraph. Accordingly, reconsideration and withdrawal of the rejection of claims 1, 15, 24 and 25 under 35 U.S.C. §112, second paragraph, is respectfully requested.

The Rejections under 35 U.S.C. §102:

Claims 1, 12-14 and 24-27 were rejected under 35 U.S.C. §102(a) as anticipated by Mohammadi. In particular, the Office asserts that Mohammadi describes "an enhancerless positive feedback regulatory vector construct pSaiIV transcribing both the tetracycline-controlled transactivator (tTA) and mGM-CSF from a modified tTA-responsive bidirectional promoter." Applicant respectfully traverses the rejection.

Initially, applicant notes that the publication date for Mohammadi appears to be sometime in 1998. Since applicant has claimed, and is in fact entitled to priority to his 19 October 1998 filing, it is believed that Mohammadi is not properly citable as prior art. Clarification of the actual publication date of the Mohammadi reference is thus respectfully requested.

If the Mohammadi reference is indeed properly citable as prior art, applicant draws the Office's attention to claims 1 and 12-14, all of which require the transfer into a mammalian cell of a nucleic acid construct comprising a minimal promoter sequence linked to a coding sequence for an antigen of interest. Mohammadi would clearly fail to anticipate these claims since there is no disclosure of a minimal promoter linked to an antigen-encoding sequence. It is well established that, to be anticipatory under Section 102, a cited reference must disclose within its four corners each and every element of the claimed invention. Since Mohammadi fails to disclose applicant's recited methods, it cannot anticipate claims 1 and 12-14. Accordingly, reconsideration and withdrawal of the rejection of these claims under 35 U.S.C. §102(a) is earnestly solicited.

Claim 24 recites a purified, isolated minimal promoter sequence. Applicant cannot find any disclosure of a purified and isolated minimal promoter sequence anywhere in the Mohammadi reference. Accordingly, it is submitted that Mahammadi cannot anticipate claim 24. Reconsideration and withdrawal of the rejection of this claim under 35 U.S.C. §102(a) is thus respectfully requested.

Claims 25-27 recited constructs containing a minimal promoter operably linked to a coding sequence for an antigen of interest. Mohammadi fails to disclose such constructs, and therefore cannot anticipate claims 25-27. Accordingly, reconsideration and withdrawal of the rejection of these claims under 35 U.S.C. §102(a) is earnestly solicited.

Claims 1, 12-14 and 24-27 stand rejected under 35 U.S.C. 102(b) as anticipated by Hofmann. The Office asserts that Hofmann describes "a recombinant retroviral vector construct (SIN-RetroTet vector) containing an autoregulatory cassette comprising a heptamerized tet operator sequence fused to the human CMV immediate

early minimal promoter." The Office thus concludes that the claims are anticipated by the reference. Applicant respectfully traverses.

Here again, applicant draws the Office's attention to claims 1 and 12-14, all of which require the transfer into a mammalian cell of a nucleic acid construct comprising a minimal promoter sequence linked to a coding sequence for an antigen of interest. Hofmann fails to anticipate these claims since there is no disclosure of a minimal promoter linked to an antigen-encoding sequence. Accordingly, reconsideration and withdrawal of the rejection of these claims under 35 U.S.C. §102(b) is earnestly solicited.

Claim 24 recites a purified, isolated minimal promoter sequence. Applicant cannot find any disclosure of a purified and isolated minimal promoter sequence anywhere in the Hofmann reference. Accordingly, it is submitted that Hofmann cannot anticipate claim 24. Reconsideration and withdrawal of the rejection of this claim under 35 U.S.C. §102(b) is thus respectfully requested.

Claims 25-27 recite constructs containing a minimal promoter operably linked to a coding sequence for an antigen of interest. Hofmann fails to disclose such constructs, and therefore cannot anticipate claims 25-27. Accordingly, reconsideration and withdrawal of the rejection of these claims under 35 U.S.C. §102(b) is earnestly solicited.

Claims 1-4, 7-8, 11-17, 20-23 and 25-27 were rejected under 35 U.S.C. §102(b) as anticipated by Lai. The Office asserts that Lai describes "a vaccine DNA construct comprising a DNA fragment of *Mycoplasma pulmonis* under the control of the CMV immediate early promoter." The Office states that it reads "the open language of the term 'comprising' in the claims as encompassing enhancer elements in addition to a minimal promoter sequence." Office Action at page 15. Applicant respectfully traverses.

Anticipation of a claim under §102 *requires* that each and every element of the claims be inherent in, or disclosed expressly by the anticipating reference. *Constant v. Advanced Micro-Devices, Inc.*, 7 USPQ2d 1057, 1064 (Fed. Cir. 1988). Exclusion of a single claimed element from a prior art reference is enough to negate

anticipation by that reference. *Atlas Powder Co. v E.I. du Pont De Nemours & Co.* 224 USPQ 409, 411 (Fed. Cir. 1984). Further, anticipation basically requires identity with the prior art document *(Tyler Refrigeration v. Kysor Indus. Corp.*, 227 USPQ 845 (Fed. Cir. 1985)), where the identical invention must be shown in as complete detail as is contained in the rejected claim (*Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913 (Fed. Cir. 1989)). Finally, in order to anticipate, a prior art reference must be enabling, thus placing the allegedly disclosed matter in the possession of the public. *Akzo N.V. v. United States ITC*, 1 USPQ2d 1241 (Fed. Cir. 1986).

In the instant rejection, the Office has ignored the clear language of the claims. All of applicant's claims include the limitation that there is a minimal promoter sequence used. This term is clearly and unambiguously defined in the specification as only those promoters where the native enhancer sequence has been excised or otherwise removed. The vector construct described by Lai clearly includes a promoter sequence that is coupled with its native enhancer sequence. Lai therefore cannot possibly anticipate any of applicant's claims, since each and every element of applicant's claims are **NOT** inherent in, **NOR** disclosed expressly by the anticipating reference and there is **NO** identity between applicant's recited methods and reagents and the fully enhanced CMV promoter system described by Lai. Reconsideration and withdrawal of the rejection of claims 1-4, 7-8, 11-17, 20-23 and 25-27 under 35 U.S.C. §102(b) is thus earnestly solicited.

Claims 1, 5, 7, 8 and 12 stand rejected under 35 U.S.C. §102(b) as anticipated by Laube. The Office asserts that Laube describes *"ex vivo* transduction of autologous non-human primate rhesus monkey fibroblasts .. with a retroviral vector encoding HIV-1 IIIB ENV/REV proteins." Here again, the Office asserts that applicant's claims encompass promoters coupled with native enhancer sequences, and that Laube's fully enhanced promoters thus anticipate. Applicant respectfully traverses.

As discussed above, the Office has ignored the clear language of the claims. All of applicant's claims include the limitation that there is a minimal promoter sequence used. This term is clearly and unambiguously defined in the

specification as only those promoters where the native enhancer sequence has been excised or otherwise removed. The vector construct described by Laube clearly includes a promoter sequence that is coupled with its native enhancer sequence. Laube therefore cannot possibly anticipate any of applicant's claims, since each and every element of applicant's claims are **NOT** inherent in, **NOR** disclosed expressly by the anticipating reference and there is **NO** identity between applicant's recited methods and reagents and the fully enhanced CMV promoter system described by Laube. Reconsideration and withdrawal of the rejection of claims 1, 5, 7-8 and 12 under 35 U.S.C. §102(b) is thus earnestly solicited.

CONCLUSION

Applicant respectfully submits that the claims define an invention which complies with the requirements of 35 U.S.C. § 112 and which is novel and nonobvious over the art. Accordingly, allowance is believed to be in order and an early notification to that effect would be appreciated. The examiner is requested to contact the undersigned at (510) 742-9700, ext. 209, should there be any remaining issues that can be dealt with over telephone.

Respectfully submitted,

Date: 4 April 2001

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